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PAEDIATRIC CLINICAL PHARMACOLOGY

Development of one paediatric and one neonatal formulary list in hospital settings

Correspondence Helle Holst, MD, PhD, MSc Paediatric Medicine, Department of Clinical Pharmacology, Bispebjerg Hospital, 2400 Copenhagen, Denmark. Tel.: +45 3531 2703; Fax: +45 3531 3711; E-mail: helle.holst.01@regionh.dk

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Sissel Sundell Haslund-Krog[1], Hanne Rolighed Christensen[1], Mia Bjerager[2] and Helle Holst[1]

[1]Department of Clinical Pharmacology, Bispebjerg Hospital, 2400 Copenhagen, Denmark and [2]Department of Paediatric and Adolescent Medicine, Nordsjællands Hospital Hillerød, 3400 Hillerød, Denmark

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AIMS

The aim of this study is to describe the stepwise process towards creating two formulary lists: one for paediatric and one for neonatal patients covering common diseases in hospital settings.

METHODS

This study presents the concept for developing a formulary list, namely how to: (1) organize the editorial board, (2) procure drug consumption data and database management, including information on labelling status, dosing options, excipients and problematic adverse events, current guidelines, evidence and price, (3) develop the first edition for the formulary list and formulary manual, and (4) to establish a paediatric sub-committee within the Regional Drug and Therapeutic Committee to maintain and continually develop the two formularies.

RESULTS

The total number of drugs was 411 ATC level 5, which covers 1097 unique item numbers prior to the paediatric formulary list, of which 263 item numbers were included in the final list. In neonates, 201 drugs ATC level 5 were evaluated, covering 348 unique item numbers, of which 104 item numbers were included in the final neonatal formulary list. Eighty-eight percent of the included drugs in the paediatric formulary were licensed to children (not specified by age group), 2% were unlicensed in Denmark, and 7% were extemporaneous preparations. For neonates, the percentage was 48%, 4% and 16%, correspondingly.

CONCLUSION

The process is time-consuming as studies are lacking and age-appropriate dosage forms and concentrations differ amongst countries. Nevertheless, the process should be somewhat similar between countries, albeit different drugs may be selected for the final formulary lists.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Few countries have a formulary to guide prescription. Those that do include the UK (BNF), the Netherlands (Kinderformularium) and Sweden.
- Standard treatment guidelines do not necessarily choose between analogue drugs.
- Unlicensed and extemporaneous drugs are necessary in formularies to meet the medicinal needs of all age groups.

WHAT THIS STUDY ADDS

- In order to ensure ownership and facilitate implementation, the formulary should be based on drug consumption data and aligned with standard treatment guidelines.
- A separate neonatal formulary is recommended.
- Evaluation of drug substances is required on a detailed ATC level, as age approval and drug availability differ amongst countries.

Introduction

According to the World Health Organization (WHO), 'Rational drug use requires that the patients receive drugs appropriate to their clinical needs in doses that meet their individual requirements (right dose, right intervals and right duration)' [1]. In order to achieve this goal and improve quality of care, it is important that common diseases are treated with few cost-effective medicines. The selection of these essential medicines should be based on standard treatment guidelines (STGs), treatment algorithms and drug consumption data [1], thereby creating a 'formulary list'. The process of selecting medicines should be transparent, that is, a public formulary manual should be available, involve all stakeholders, and be driven and monitored by a Drug and Therapeutics Committee (DTC) [1, 2]. This concept was originally introduced by the WHO for adult medicine in the 1970s [3] and has been implemented in Denmark for more than two decades. In 2007, the WHO introduced a similar model list for essential medicines for children [3]. In contrast to adults, less than 50% of authorized medicines commonly used for children and adolescents have been appropriately tested in this population [4–6]. Off-label use and use of unlicensed products may lead to suboptimal treatment and exposes children to unknown risks of adverse events [7]. For example, some excipients added to the active ingredient are particularly harmful in neonates [8] which might not be common knowledge for all clinicians. Hence, efficacy data is required for each age group in order to support drug selection, as are safety data [9, 10]. Different initiatives exist around Europe to support paediatric prescriptions. In Sweden, two formulary lists exists: one developed by The Stockholm County Council [11] and one by the Uppsala-Örebro County [12]. In the UK, a more comprehensive version of all available drugs is updated annually, and is known as the British National Formulary for Children (BNFc), which also includes neonates [13]. The work of BNFc has partly been adopted by the Medicines for Children Network, established in 2009 in Norway [14]. In the Netherlands Kinderformularium [15] similarly advise treatment regimens. In Denmark no such comparable initiative existed, and was requested by the paediatricians since a survey revealed that comparable paediatric departments used various and different drugs. Albeit, different drugs may be selected for the final formulary list, the process should be somewhat similar between countries.

This study aims to describe the stepwise process towards creating two formulary lists: one for paediatric and one for neonatal patients covering common diseases in hospital settings.

Methods

The Regional Council in the Capital Region of Denmark funded a three-year project (2014–2016) to facilitate the development of formulary lists for neonates and children. The overall annual budget was €133.333. This project did not require formal ethical approval.

Step 1: Organizing the editorial board

A core team of a clinical pharmacologist subspecialized in paediatric pharmacology (project manager, 0.3 fulltime equivalent (fte)), a junior doctor (1.0 fte), and a pharmacist (0.1 fte) at Department of Clinical Pharmacology, Bispebjerg Hospital, Copenhagen University, Denmark, coordinated the project. The pharmacists assisted in prices and availability of drugs. The council for paediatrics and neonatology appointed specialists in all paediatric fields from four university hospitals in the Capital Region to support the project. Hence, one paediatric expert and one neonatologist were appointed for, e.g. drugs used in diabetes, as part of the Anatomical Group A 'Alimentary tract and metabolism' (ATC A), etc. [16]. The 21 members of the editorial board were not paid.

Step 2: Procuring drug consumption data and database management

Information on purchased medicine from all paediatric and neonatal departments from 2014 to 2015 were procured from the regional pharmacy database. Data comprise defined daily dosages (DDD), formulations, packages, strengths and costs. The DDD system is managed and maintained by the WHO [17]. No specific paediatric DDD exists, except for somatropin. Accordingly, the DDD can only be used as an analytical tool to ensure drug utilization data from all departments for the initial selection of essential medicines.

For limitations, see [18]. In total the four paediatric departments cover 35 sections and the four neonatal departments cover five sections. The Board agreed that drug substances used exclusively in the specialized sections, e.g. paediatric oncology and extreme premature neonates, were excluded from the next steps. In consequence, ATC G (genito-urinary system and sex hormones), V (various), and L (antineoplastic and immunomodulating agents) were excluded due to little relevance for the common paediatric and neonatal patient.

The database management system was constructed using Microsoft Excel® version 2010. Drug substances were aligned according to the ATC classification system, which includes information on ATC levels 1 to 5, e.g. with the fifth level being information on chemical substance [19]. Since the latter does not include available formulations, packages and strengths, a new set of data were drawn on a more detailed level for all drug substances (see Figure 1), hereafter referred to as detailed ATC level best described by item numbers (i.e., unique drug substances, formulation and strength).

Apart from the inclusion of drugs based on the extent of use, the evaluation of each drug substance was qualitatively based on labelling status, obtained from the newest Summary of Product Characteristics (SmPC) at the Danish Health and Medicines Authority website, or in the case of central approval, on the European Medicine Agency (EMA) website [20, 21]. If labelling status was unclear, the company holding the marketing approval was contacted. For example, the phrase in the SmPC is often unclear if: ages are not provided as numerals, the term 'children' is used, or preterm and term neonates are not specifically mentioned [22]. Drugs substances used at the neonatal departments were additionally evaluated regarding the content of potential harmful excipients. **Ethanol**, benzyl alcohol, propylene glycol, polysorbate, aspartame, parabens, **benzoates**, benzalkonium chloride and sorbitol were considered potentially harmful excipients in accordance with the Safety and Toxicity of Excipients for Paediatrics (STEP) database [23]. If content of excipients was not specified in the SmPC, the company holding the marketing approval was contacted. In case of extemporaneous prepared drugs, the pharmacy producing the medicine was contacted. If two products we equally appropriate for the paediatric or neonatal population, the costs were also included in step 2 (see Figure 2).

Standard operating procedures (SOP) for each of the activities were also described in detail at this step, i.e. for handling and sorting DDD data, for literature search including how to interpret data from the SmPC (see above), for selection and evaluation of drug substances, and for the visual look and contents of the formulary manuals and for the paediatric and neonatal formularies, respectively.

Step 3: Formulary list and formulary manual

For every ATC group a consensus meeting was held with the paediatric and the neonatal specialists. Neonates were defined as the period from birth up to 44 full weeks post menstrual age [24].

A week before the meeting the specialist received the SOP for selection and evaluation of the drug substances together with the preliminary list with all gathered information on the drug substances including available STGs [1]. STGs do not necessarily choose between analogue drugs; this was done when developing the formulary lists. All references, answers from medicinal companies, and decisions were documented in the publicly available formulary manual (in Danish) (see Figure 3). If no appropriate marketed alternative existed (licensed or unlicensed, i.e. imported from another country), the available extemporaneous products were evaluated.

Each formulary list includes: ATC groups; ATC A (alimentary tract and metabolism), B (blood and blood forming organs), C (cardiovascular system), D (dermatologicals), H (systemic hormonal preparations), J (anti-infectives for systemic use), M (musculo-skeletal system), N (nervous system), P (antiparasitic products), R (respiratory system)

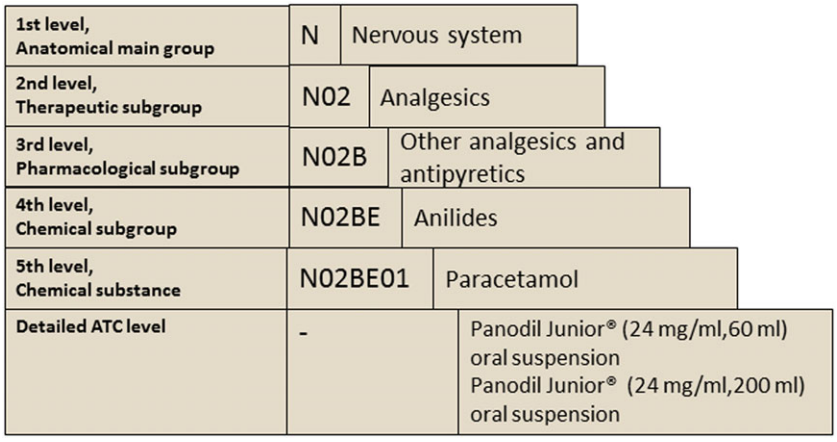


Figure 1

Illustration of the Anatomical Therapeutic Chemical (ATC) classification system and ATC codes, including the detailed ATC level which include formulation, strength and packages of the drug substance

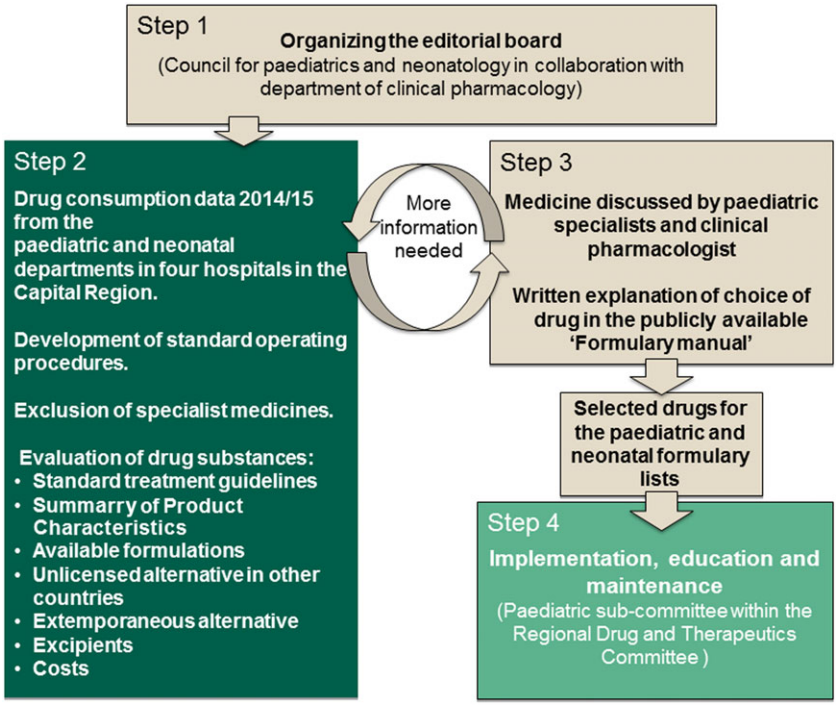


Figure 2

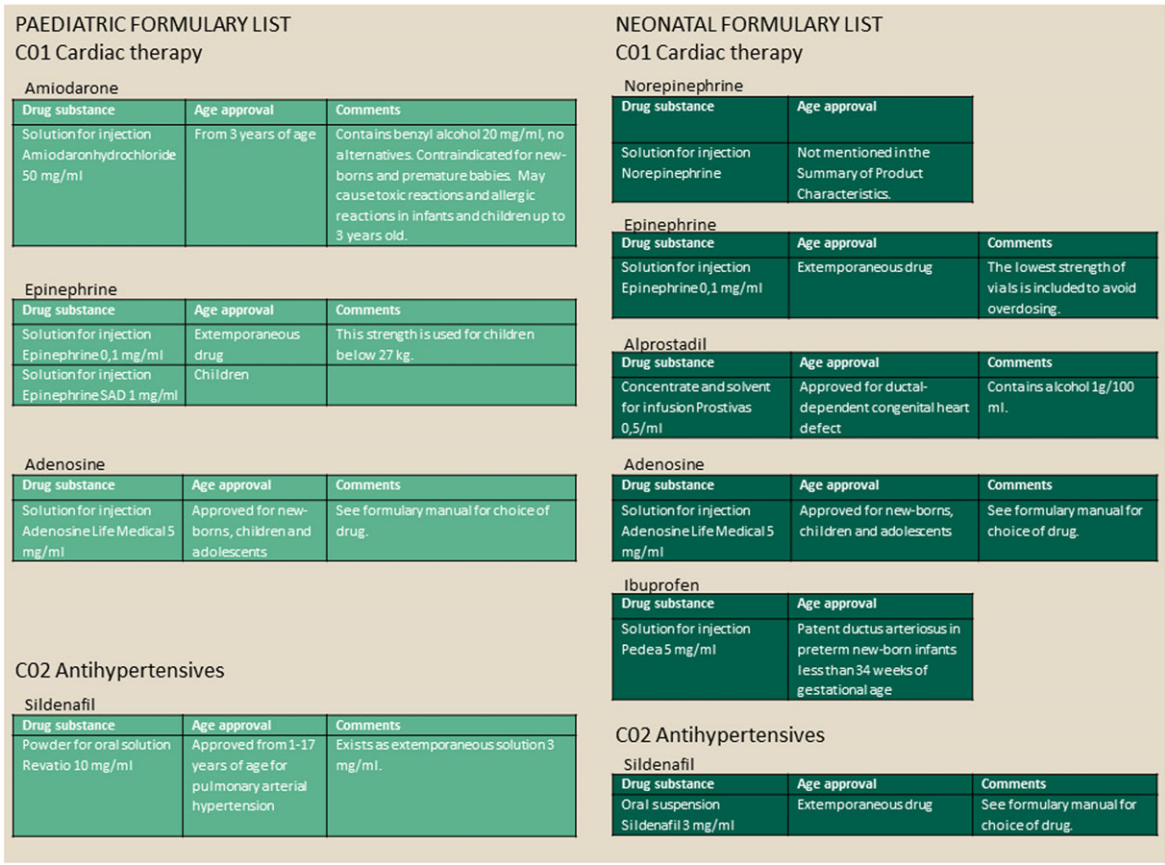
The stepwise process of developing one paediatric and one neonatal formulary list

FORMULARY MANUAL	
C01 Cardiac therapy	
ATC code and drug substance	**Decision**
C01AA05 Digoxin	Not included. Rarely used. The i.v. product contains ethanol 100 mg/ml, the oral solution contains less than 5 mg/ml of ethanol. Approved for premature- and mature new-borns, infants and children.
C01BA01 Quinidine	Not included. Unlicensed drug substance. Classified as specialist treatment.
C01BC04 Flecainide	Not included. Classified as specialist treatment. Extemporaneous oral solutions are prepared at Skanderborg Pharmacy.
C01BD01 Amiodarone	Included. I.v. Amiodaronhydrochloride 50 mg/ml, for the treatment of supraventricular and ventricular arrhythmias. Approved from 3 years of age, contraindicated for new-borns because of benzyl alcohol (contains 20 mg/ml), no unlicensed alternatives without benzyl alcohol.

Figure 3

Example of the formulary manual. The formulary manual contains the summarized information of all drug substances evaluated by the board including the decisions made by the board (references not shown in figure)

and S (sensory organs). The specific content of the two formularies is exemplified in Figure 4 and includes the specific drug substance, strength, the labelling status and comments for some drugs concerning special warnings, excipients, etc. The formularies are available in Danish for all hospital employees.



PAEDIATRIC FORMULARY LIST

C01 Cardiac therapy

Amiodarone

Drug substance	Age approval	Comments
Solution for injection Amiodaronhydrochloride 50 mg/ml	From 3 years of age	Contains benzyl alcohol 20 mg/ml, no alternatives. Contraindicated for new-borns and premature babies. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.

Epinephrine

Drug substance	Age approval	Comments
Solution for injection Epinephrine 0,1 mg/ml	Extemporaneous drug	This strength is used for children below 27 kg.
Solution for injection Epinephrine SAD 1 mg/ml	Children	

Adenosine

Drug substance	Age approval	Comments
Solution for injection Adenosine Life Medical 5 mg/ml	Approved for new-borns, children and adolescents	See formulary manual for choice of drug.

C02 Antihypertensives

Sildenafil

Drug substance	Age approval	Comments
Powder for oral solution Revatio 10 mg/ml	Approved from 1-17 years of age for pulmonary arterial hypertension	Exists as extemporaneous solution 3 mg/ml.

NEONATAL FORMULARY LIST

C01 Cardiac therapy

Norepinephrine

Drug substance	Age approval
Solution for injection Norepinephrine	Not mentioned in the Summary of Product Characteristics.

Epinephrine

Drug substance	Age approval	Comments
Solution for injection Epinephrine 0,1 mg/ml	Extemporaneous drug	The lowest strength of vials is included to avoid overdosing.

Alprostadil

Drug substance	Age approval	Comments
Concentrate and solvent for infusion Prostivas 0,5/ml	Approved for ductal-dependent congenital heart defect	Contains alcohol 1g/100 ml.

Adenosine

Drug substance	Age approval	Comments
Solution for injection Adenosine Life Medical 5 mg/ml	Approved for new-borns, children and adolescents	See formulary manual for choice of drug.

Ibuprofen

Drug substance	Age approval
Solution for injection Pedea 5 mg/ml	Patent ductus arteriosus in preterm new-born infants less than 34 weeks of gestational age

C02 Antihypertensives

Sildenafil

Drug substance	Age approval	Comments
Oral suspension Sildenafil 3 mg/ml	Extemporaneous drug	See formulary manual for choice of drug.

Figure 4

Example of the paediatric and neonatal formulary lists. The formularies contain the specific drug substance, strength, age approval and comments

Example of an evaluation for a licensed product: Paracetamol

Paracetamol for treatment of fever and acute mild–moderate pain for paediatric patients was used in nine different forms of administration (e.g., suppositories, oral solutions or suspensions, conventional tablets, etc.), as 20 different item numbers (e.g., Pinex Junior®, Panodil Junoir®, Pamol®, etc.), in different strengths (e.g. 125 mg, 250 mg, 24 mg ml^{-1}, 500 mg, etc.). Of these, four administration forms were chosen (conventional tablet, oral solution, oro-dispersible tablets and suppositories) as suitable for the paediatric formulary list covering six different item numbers (i.e. tablet Pamol® 500 mg, oro-dispersible tablet Pamol flash® 250 mg, Oral solution Pinex Junior® 24 mg ml^{-1}, Paracetamol suppositories 50 mg, Pinex® or Panodil® suppositories 125 and 250 mg).

For another example, see Supporting information.

Step 4: Implementation and education

As a consequence of the work with the paediatric and neonatal formulary lists, the Council for Paediatrics and Neonatology have agreed to establish a paediatric subcommittee within the Regional Drug and Therapeutics committee to implement, update and maintain the formulary lists. The members will consist of a clinical pharmacologist subspecialized in paediatric pharmacology (Chair), a paediatrician appointed by the Regional Council for Paediatrics and Neonatology (Co-Chair), one paediatrician or neonatologist from each hospital, two paediatric nurses, two pharmacists and a representative from the regional DTC. The secretary of the regional DTC will serve the paediatric committee. The Committee will meet four times annually. The primary goals and objectives will be to ensure that only efficacious, safe, cost-effective and good quality medicines are used by constantly reviewing the current formulary lists, by facilitating education in paediatric pharmacology, and by focusing on preventable adverse drug reactions (ADRs) and medication errors.

Nomenclature of targets and ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [25].

Results

The total number of drugs evaluated was 411 ATC level 5, which covers 1097 unique item numbers prior to the

paediatric formulary list, of which 263 item numbers were included in the final list (see Table 1). In neonates, 201 drugs ATC level 5 were evaluated covering 348 unique item numbers, of which 104 item numbers were included in the final neonatal formulary list (see Table 1). In total, 88% of the drugs included in the paediatric formulary list were licensed for children (not specified by age group), 2% were unlicensed in Denmark, and 7% were extemporaneous preparations made by two pharmacies. The remaining 3% were off label according to the Danish SmPCs (not shown in Table 1a). For neonates, the percentage was 48%, 4% and 16%, correspondingly. The remaining 32% were off label according to the Danish SmPCs (not shown in Table 1b).

For all ATC groups a substantial reduction in the number of drug formulations was possible, without compromising the need for various formulations and strengths for common and acute diseases. The greatest reduction was made in ATC N (Nervous system) in both formularies, with a reduction from

Table 1

Total number of drugs (ATC level 5) and item numbers (detailed ATC level, i.e. formulation and strength) prior to and included in the paediatric and neonatal formularies. The percentages of drugs being licensed, unlicensed, and extemporaneously prepared are shown in separate columns.

1a. Paediatric departments

ATC group	Unique item numbers prior to the paediatric formulary list (ATC level 5)	Unique item numbers in the paediatric formulary list	No. of drugs licensed for children in Denmark, *n* (%)[a]	Unlicensed drugs, *n* (%)	Extemporaneous drugs, *n* (%)
A	118 (83)	25	24	0	1
B	175 (40)	37	37	0	0
C	81 (44)	30	15	0	6
D	50 (38)	21	21	0	0
H	83 (18)	15	10	1	4
J	212 (55)	59	58	1	0
M	35 (18)	6	3	3	0
N	248 (65)	27	23	0	4
P	9 (4)	8	6	0	2
R	63 (29)	28	28	0	0
S	23 (17)	7	6	1	0
Total	**1097 (411)**	**263**	**231 (88%)**	**6 (2%)**	**17 (7%)**

1b. Neonatal departments

ATC group	Unique item numbers prior to the neonatal formulary list (ATC level 5)	Unique item numbers in the neonatal formulary list	Drugs licensed for neonates in Denmark, *n* (%)	Unlicensed drugs, *n* (%)	Extemporaneous drugs, *n* (%)
A	46 (37)	14	5	1	1
B	60 (26)	15	4	0	2
C	39 (23)	15	7	0	7
D	32 (24)	13	5	0	0
H	18 (8)	2	1	0	1
J	39 (24)	18	14	2	0
M	10 (7)	2	2	0	0
N	70 (30)	17	10	0	5
P[b]	0	0	0	0	0
R	19 (14)	1	1	0	0
S	15 (8)	7	1	1	1
Total	**348 (201)**	**104**	**50 (48%)**	**4 (4%)**	**17 (16%)**

[a]Does not distinguish between licence for all paediatric age groups or only a subgroup.
[b]The only drug included is intravenous metronidazole which is a part of ATC group J in accordance with the ATC system.
Anatomical Therapeutic Chemical (ATC)

248 item numbers to 27 (89% reduction) in the paediatric formulary list and from 70 item numbers to 17 (75% reduction) in the neonatal formulary list.

Marketing holders were contacted for clarification on age approval or excipient content. Adding up to a total of 37 correspondences primarily on matters of age approvals, 128 manufacturers were contacted to obtain excipient information and 26 comments were made regarding excipients in the neonatal formulary list. Further, an overview of the ten most well-known harmful excipients and their threshold for toxicity were added in the neonatal formulary appendix.

Discussion

Rational drug use

The overall goal of the paediatric and neonatal formularies are to support paediatric prescriptions concerning dose tailoring, evidence-based treatment, safety and costs. This concept combines clear principles for rational drug use [26]. Just as important, the process must be transparent, consensus-based with an offset in drug consumption in the clinical settings and standard treatment guidelines, in order to ensure ownership and henceforward use [1]. Fewer drug formulations will enhance familiarity with the ones chosen and diminish the risk of medication errors, as the latter has often been linked to dosing errors and formulations [27].

Thus far, the paediatric and neonatal formulary lists have been presented to the staff at the paediatric and neonatal wards at all hospitals, to inform about the stepwise process for developing the two lists, as well as to ensure that each department was given a chance to comment on the lists. This has been a fruitful and fundamental co-operation adding different perspectives to the drug evaluation process. The core team did also meet with the Hospital Drug Services in order to ensure the lists could be efficiently implemented [28]. In general, both clinicians and non-clinical staff have received the lists positively. Since dosages guidelines were not part of the presented lists, this issue was discussed in depth with the medical doctors. The lack of evidenced-based drug monographs containing information regarding paediatric prescribing is clearly a threat to safe and effective medicine use [29]. This step will be very time-consuming, will require national collaboration, was not feasible within the initial 3-year funding and is an obvious limitation of this project. To illustrate the complexity, we here provide three different recommendations for orally administered paracetamol according to: the Swedish list from the Uppsala-Örebro County—10–15 mg kg^{-1} × 4 for children >3 months [30]; the Kinderformularium—90 mg kg^{-1} day^{-1} in four doses for children >1 month [15]; and the BNFc—Child 1–2 months, 30–60 mg every 8th hour maximum 60 mg kg^{-1} day^{-1}, child 3–5 months maximum 60 mg × 4 per day [31]. Hence, there is no international consensus about which dosing guidelines should be adopted. This may also be difficult to achieve, as drug use will be somewhat based on extensive national clinical experience due to a lack of studies. Moreover, drug policies may vary between countries (e.g. use of antibiotics). Further, it is often difficult to conclude whether a drug is used off label, for example in relation to age, as generics may have been authorized for different age groups by various national stakeholders [22, 32].

Another challenge is that the availability of drug formulations varies between countries [33, 34] For example, flucloxacillin oral solution, **ibuprofen** suppositories and oral solution is marketed in Sweden but not in Denmark [35]. Drug substitution with unlicensed drugs is not always feasible in small countries due to unstable drug supply, the extra procedure of applying for a compassionate use permit, and the package leaflet written in a different language. Further, the permission for compassionate use is only granted to a specific hospital department, i.e. the drug is not available for outpatient use. This is reflected in the relative small fraction of unlicensed drugs included in the formularies (see Table 1). Extemporaneous formulations are sometimes used in such cases; such use is problematic and should be limited as much as possible due to lack of studies. However, for some neonatal drugs the extemporaneous formulation was superior to the licensed formulation with regard to content of excipients (e.g. **Oramoph®**). The low strength Oramorph® formulation (2 mg ml^{-1}) appropriate for children contains 0.105 ml alcohol per ml [36], while the high strength oral drops (20 mg ml^{-1}) inappropriate in paediatric settings is alcohol free, as is the extemporaneous alternative Opium drops 4 mg ml^{-1} (internal data). We consider alcohol-free replacements ethically crucial, bearing in mind the examples of elevated **acetaldehyde** measured in neonates [37] and exposure of ethanol to neonates with chronic lung disease [38], supporting the need for a separate neonatal formulary.

Equal access to child size medicine for all children in the EU is still the goal of paediatric regulation. Our data show scarcity of licensed paediatric formulations which necessitates use of unlicensed and extemporaneous drugs in a formulary, since, for example, **losartan** liquid formulations of antihypertensive medicines are not licensed in Denmark even though the product is licensed in all other EU countries [39].

These first editions of the formularies cover paediatric and neonatal drug use in hospital care.

Maintaining and improving a formulary is an ongoing process that will be further planned when the work of the paediatric committee is commencing. A paediatric formulary for outpatient care is a long-term goal for the paediatric committee. However, the reimbursement system is different in primary care; therefore, is not always possible to include the same generics in the two settings and will require a separate formulary list.

Conclusion

We developed first editions of one paediatric and one neonatal formulary. The stepwise process towards a best evidence formulary has previously been described for adults but is somewhat different in neonates and children. The process is time-consuming as studies are lacking and age-appropriate dosage forms and concentrations differ amongst countries. Nevertheless, the process should be somewhat similar between countries and knowledge should be shared internationally. In the future, a pan-European formulary is warranted.

Competing Interests

There are no competing interests to declare.

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References

1 World Health Organization. Drug and therapeutics committees – a practical guide [online]. 2006. Available at http://apps.who.int/medicinedocs/en/d/Js4882e/ (last accessed 10 August 2017).

2 Gustafsson LL, Wettermark B, Godman B, Andersén-Karlsson E, Bergman U, Hasselström J, *et al*. The 'Wise List' – a comprehensive concept to select, communicate and achieve adherence to recommendations of essential drugs in ambulatory care in Stockholm. Basic Clin Pharmacol Toxicol 2011; 108: 224–33.

3 WHO. WHO model lists of essential medicines [online]. Available at http://www.who.int/medicines/publications/essentialmedicines/en/ (last accessed 25 November 2013).

4 Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, *et al*. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. BMJ 2000; 320: 79–82.

5 't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. Unapproved and off-label use of drugs in a children's hospital. N Engl J Med 2000; 343: 1125.

6 't Jong GW, Vulto AG, de Hoog M, Schimmel KJ, Tibboel D, van den Anker JN. A survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001; 108: 1089–93.

7 van der Zanden TM, de Wildt SN, Liem Y, Offringa M, de Hoog M. Dutch Paediatric Pharmacotherapy Expertise Network NKFK (Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen). Developing a paediatric drug formulary for the Netherlands. Arch Dis Child 2017; 102: 357–61.

8 Nellis G, Metsvaht T, Varendi H, Toompere K, Lass J, Mesek I, *et al*. Potentially harmful excipients in neonatal medicines: a pan-European observational study. Arch Dis Child 2015; 100: 694–9.

9 Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med 2003; 349: 1157–67.

10 Murphy MD, Cope J, Iyasu S. Pharmacovigilance in pediatrics. In: Mann's Pharmacovigilance, 3rd edn, eds Andrews EB, Moore N. Hoboken, NJ: Wiley-Blackwell, 2014; 625–37.

11 The Wise List 2015 in English – Janusinfo [online]. Available at http://www.janusinfo.se/In-English/The-Wise-List-2015-in-English/ (last accessed 8 September 2017).

12 Rekommenderade läkemedel för barn [online]. Available at http://www.lul.se/sv/Extranat/For_vardgivare/Lakemedelskommitten/Rekommenderade-lakemedel/Rekommenderade-lakemedel-for-barn/ (last accessed 28 June 2016).

13 BNF Publications. British National Formulary for Children [online]. Available at https://www.bnf.org/products/books/ (last accessed 2 January 2017).

14 Norwegian National Network for Children's Medicine [online]. Available at https://www.legemidlertilbarn.no/Sider/default.aspx (last accessed 28 June 2016).

15 Kinderformularium.nl [online]. Available at http://kinderformularium.nl/search/index.php (last accessed 22 February 2013).

16 WHOCC – ATC/DDD Index [online]. Available at https://www.whocc.no/atc_ddd_index/ (last accessed 8 September 2017).

17 WHOCC – Use of ATC/DDD [online]. Available at http://www.whocc.no/use_of_atc_ddd/ (last accessed 22 February 2013).

18 Haslund-Krog S, Mathiasen R, Christensen HR, Holst H. The impact of legislation on drug substances used off-label in paediatric wards – a nationwide study. Eur J Clin Pharmacol 2014; 70: 445–52.

19 WHOCC – Structure and principles [online]. Available at http://www.whocc.no/atc/structure_and_principles/ (last accessed 16 November 2016).

20 European Medicines Agency. European public assessment reports [online]. Available at http%3A%2F%2Fwww.ema.europa.eu%2Fema%2Findex.jsp%3Fcurl%3Dpages%2Fmedicines%2Flanding%2Fepar_search.jsp%26amp%3Bmid%3DWC0b01ac058001d124 (last accessed 8 March 2013).

21 Danish Medicines Agency. Summary of product characteristics [online]. Available at http://www.produktresume.dk/docushare/dsweb/View/Collection-96 (last accessed 2 January 2017).

22 Wimmer S, Neubert A, Rascher W. The safety of drug therapy in children. Dtsch Arztebl Int 2015; 112: 781–7.

23 EuPFI [online]. Available at http://www.eupfi.org/ (last accessed 4 July 2016).

24 Ward RM, Benjamin D, Barrett JS, Allegaert K, Portman R, Davis JM, *et al*. Safety, dosing, and pharmaceutical quality for studies that evaluate medicinal products (including biological products) in neonates. Pediatr Res 2017; 81: 692–711.

25 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH, *et al*. The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: Towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

26 Eriksen J, Gustafsson LL, Ateva K, Bastholm-Rahmner P, Ovesjö M-L, Jirlow M, *et al*. High adherence to the 'Wise List' treatment recommendations in Stockholm: a 15-year retrospective review of a multifaceted approach promoting rational use of medicines. BMJ Open 2017; 7: e014345.

27 Wong ICK, Ghaleb MA, Franklin BD, Barber N. Incidence and nature of dosing errors in paediatric medications: a systematic review. Drug Saf 2004; 27: 661–70.

28 Management Sciences for Health. Managing Drug Supply, 2nd ed.) edn. West Hartford, CT: Kumarian Press, 1997.

29 Kelly LE, Ito S, Woods D, Nunn AJ, Taketomo C, de Hoog M, *et al*. A comprehensive list of items to be included on a pediatric drug monograph. J Pediatr Pharmacol Ther 2017; 22: 48–59.

30 Rekommenderade läkemedel för barn 2017–2018 [online]. Available at https://www.regionuppsala.se/Global/Extran%C3%A4t/V%C3%A5rdgivare/L%C3%A4kemedelsenheten/

Dokument/Reklista_barn/Reklista_barn_2017-18_webb.pdf (last accessed 11 September 2017).

31 bnfc.org. BNF for children, 2015–2016 edn. London: BMJ Group.

32 Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol 2013; 14: 1.

33 Reidenberg MM. World Health Organization program for the selection and use of essential medicines. Clin Pharmacol Ther 2007; 81: 603–6.

34 Bajcetic M, Kearns GL, Jovanovic I, Brajovic M, van den Anker JN. Availability of oral formulations labeled for use in young children in Serbia, Germany and the USA. Curr Pharm Des 2015; 21: 5668–73.

35 Läkemedelsverket/Medical Products Agency [online]. Available at https://lakemedelsverket.se/ (last accessed 11 September 2017).

36 Danish Mediciens Agency. Summary of product characteristics. Oramorph, oral opløsning 2mg/ml. 3. Marts 2016. [online]. Available at www.produktresume.dk (last accessed 10 October 2016).

37 Pandya HC, Mulla H, Hubbard M, Cordell RL, Monks PS, Yakkundi S, *et al*. Essential medicines containing ethanol elevate blood acetaldehyde concentrations in neonates. Eur J Pediatr 2016; 175: 841–7.

38 Whittaker A, Currie AE, Turner MA, Field DJ, Mulla H, Pandya HC. Toxic additives in medication for preterm infants. Arch Dis Child Fetal Neonatal Ed 2009; 94: F236–40.

39 10-year Report to the European Commission. General report on the experience acquired as a result of the application of the Paediatric Regulation. Prepared by the European Medicines Agency and its Paediatric Committee [online]. Available at http://ec.europa.eu/health//sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf (last accessed 13 February 2017).

Supporting Information

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Data S1 Example of an evaluation process: extemporaneous preparations

Table S1 Availability of drugs for hypertension (not exhaustive, *e.g.* diuretics not included and not all ACE inhibitors have been investigated in children). Paediatric investigation plan (PIP), Food and Drug Administration (FDA)